Nelfinavir (NFV, Viracept)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Powder for oral suspension: 50 mg/1 level gram scoopful (200 mg/1 level teaspoon)
(Oral powder contains 11.2 mg phenylalanine per gram of powder.)

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/infant dose:
NFV should not be used for treatment in children <2 years of age.

(See the perinatal guidelines for recommendations on use of NFV for prevention of mother-to-child transmission [PMTCT] of HIV.)

Pediatric dose (2–13 years of age):
45–55 mg/kg twice daily.

Adolescent/adult dose:
1,250 mg (five 250-mg tablets or two 625-mg tablets) twice daily.

(Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring [TDM] to guide appropriate dosing.)

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- Serum transaminase elevations

Special Instructions

- Administer NFV with meal or light snack.
- If coadministered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- NFV powder for oral suspension may be mixed with water, milk, pudding, ice cream, or formula; refrigerated mixture is stable for up to 6 hours.
- Do not mix powder with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of NFV oral powder. The scoop provided with the powder should be used for measuring. The powder and solution should be mixed in another container.
- Patients unable to swallow NFV tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, patients should mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

Metabolism

- CYP2C19 and 3A4 substrate.
- Metabolized to active M8 metabolite.
- CYP3A4 inhibitor.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* Cytochrome P (CYP)2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, ritonavir boosting does not significantly increase nelfinavir concentrations and coadministration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.
- Before nelfinavir is administered, carefully review the patient's medication profile for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea (most common). Asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NFV.html).

Pediatric Use: Nelfinavir is a protease inhibitor (PI) that has been used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in children >2 years of age. Nelfinavir is not recommended for treatment in children <2 years of age. Nelfinavir may be considered for neonatal prophylaxis of perinatal transmission in HIV-exposed infants in selected circumstances[1]. (See Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States).

Nelfinavir in combination with other antiretroviral (ARV) drugs has been extensively studied in HIV-infected children[2-9]. In randomized trials of children 2–13 years of age receiving nelfinavir as part of triple antiretroviral therapy (ART), the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior history of ART, the number of drugs included in the combination regimen, and dose of nelfinavir used. The relatively poor ability of nelfinavir to control plasma viremia in infants and children may be related in part to the ARV's reduced potency compared with other PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) as well as highly variable drug exposure and poor patient acceptance of available formulations[10-11].

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve [AUC] increased by as much as 5-fold) and decreases pharmacokinetic (PK) variability relative to the fasted state. Drug exposure may be even more unpredictable in pediatric patients than in adults because of increased clearance of nelfinavir observed in children, poor acceptance of pediatric formulation, and difficulties in taking nelfinavir with sufficient food to improve bioavailability.The pediatric powder formulation is poorly tolerated when mixed with food or formula. In the PENTA-7 trial, 35% (7 of 20) of infants started on powder at initiation of therapy were switched from the powder to crushed tablets because of difficulty administering the oral formulation to the infants[2]. A slurry made by dissolving nelfinavir tablets in water or other liquids can be administered to children who are unable to swallow tablets. The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole[12].

Nelfinavir is metabolized by multiple CYP-450 enzymes including CYP3A4 and CYP2C19. M8, the major oxidative metabolite, has *in vitro* antiviral activity comparable to the parent drug. The variability of drug exposure at any given dose is much higher for children than adults[13], which has been attributed at least in part to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children[14-15]. Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir PKs and the virologic responses to combination therapy in HIV-1-infected children. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in HIV-1-infected children[16].

Antiviral response to nelfinavir is significantly less in children younger than 2 years than in older children[7, 9, 17]. Infants have even lower drug exposures and higher variability in plasma concentrations than children who weigh <25 kg; the presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors[18-19]. For these reasons, nelfinavir is not recommended for use in children younger than 2 years. In older children and adolescents, it is unclear when to change from the recommended 45–55 mg/kg twice-daily dose to the adult dose of 1,250 mg twice daily. Doses higher than those recommended in adults may be required in some patients.

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{min}) <1.0 mcg/mL[20-22]. In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough concentrations <0.8 mcg/mL[23]. It is of note that the median age of the group with C_{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} >0.8 mcg/mL was 8.3 years[23]. TDM of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir[20, 24]. Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of TDM and appropriate dose adjustment might be even greater for children. Better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing.[15, 25]

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